Conditional Survival of Malignant Thymoma Using National Population-Based Surveillance, Epidemiology, and End Results (SEER) Registry (1973–2011)

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Introduction: Thymoma is a rare and unique tumor with a long natural history that makes it difficult to study. Consequently, there is a dearth of prospective diagnostic or therapeutic clinical trials. To our knowledge, there has not been an analysis of conditional survival of thymoma in the literature. The specific aim of this study was to study the 5-year conditional survivals of a large population of thymoma patients.

Methods: Cases of thymoma were extracted from the Surveillance, Epidemiology, and End Results registry (1973–2011) and categorized into Masaoka–Koga stage groupings. The primary outcomes compared overall survival (OS), cause specific survival (CSS), and 5-year conditional OS and CSS, by stage. OS and CSS were calculated using the Kaplan–Meier method with the log-rank test for significance using SAS v9.3. Conditional survival was the probability of surviving an additional 5 years at any point in follow-up, and used analysis of variance to test significance.

Results: A total of 2182 patients met inclusion criteria and were categorized as Masaoka–Koga stage groupings of I and IIA ("localized," 24%), IIB ("regional," 16%), III and IV ("distant," 50%), and unknown (10%). Median age was 56 (18–91), and 53% were male. Earlier stages had better OS ($p < 0.0001$) and CSS ($p < 0.0001$). Twenty-year OS for local, regional, and distant stages were 42%, 30%, and 18%, respectively. Conditional survivals remained largely unchanged throughout follow-up.

Conclusions: Conditional survival provides more relevant survival estimates for patients during follow-up. Further studies should investigate the possibility that thymoma should be considered a chronic disease.

Key Words: Thymoma, Conditional survival, SEER, Cancer survivorship

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Thymoma is a slow-growing tumor of the thymus, unique in its "benign" histology but potential for locally invasive or "malignant" behavior. Because all thymomas have malignant potential, they are not classified as benign or malignant types. Instead, they are divided into noninvasive and invasive forms for prognostic purposes. Its reported incidence is only 0.15 per 100,000 person-years.[1] This extremely rare tumor has an unusually long natural history. It is also unique in that it is a tumor that does not have an official American Joint Committee on Cancer or Union Internationale Contre le Cancer staging system, though many staging systems have been proposed for thymoma over the years since as early as 1978 by Bergh et al.[2] But very few of these have received clinical validation.[3] The staging system proposed by Masaoka et al.[4] in 1981 follows the natural history of thymoma, which initially grows locally, then infiltrates, disseminates, and metastasizes. Masaoka staging is based on the degree of invasion into surrounding organs. The International Thymic Malignancy Interest Group has formally selected the Masaoka–Koga staging system, the Koga modification of Masaoka staging, at least until a scientifically validated system is defined in the next edition of their staging manuals in 2017.[5] A collaborative effort by the International Association for the Study of Lung Cancer and the International Thymic Malignancy Interest Group is currently in the process of developing proposals for an official staging classification for thymic malignancies.[6] This is the staging system that is most often used clinically internationally and in the United States.

The rarity of thymoma makes both prospective and retrospective single-institution or multi-institution studies difficult, and the lack of an official staging system makes meta-analysis or combination of multiple data sources difficult. The Surveillance, Epidemiology, and End Results (SEER) registry, though imperfect, is a valuable source of data on rare tumors, such as thymoma. A population-based cancer registry that covers approximately 28% of the US population, the SEER registry is broadly representative of the US population. It is the largest domestic cancer registry and has multiple quality control measures that have made it an international standard of high quality cancer registries.[7] Though the SEER registry does not record information on American Joint Committee on Cancer stage, as it does for most other types of cancer, or Masaoka stage, it does have enough information on extent of disease that has been used effectively by Fernandes et al.[8] to categorize cases into Masaoka–Koga stage groupings.

No previous study in the literature has examined conditional survival of thymoma. Given the long natural history of thymoma, with overall survival (OS) reported not for 5-years but

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in the range of 10 or even 20 years, conditional survival is particularly useful. Survival is an estimate of the probability of being alive after a period of time. The quality of statistical probabilities depends on the information used in the calculations. Conditional survival is an application of conditional probability in statistics. It is different from traditional survival times because it takes advantage of the additional information: that the patient has already survived for some period of time. Conditional survival can provide a more direct answer to patients' question, such as "Now that I'm 10 years out from diagnosis, what's my expected survival for another 5 years?" This is not the same as the initial 15-year survival after diagnosis, even though 10 + 5 years is 15 years, because the 15-year estimate could not have known that this patient would live for at least 10 years. This is a question best answered as 5-year conditional survival at 10 years.

This study was designed to examine the conditional survival of thymoma in a large group of patients from the SEER database. Both OS and cause specific survival (CSS) are used in the study of conditional survivals.

MATERIALS AND METHODS

Data were extracted from the SEER database[17] for cases of malignant thymoma diagnosed between 1973 and 2011. The SEER registry only collects data on "malignant" thymomas.[1] Cases of thymoma excluding thymic carcinoma were identified by histology (International Classification of Diseases codes 8580–8585) and organ of origin (collaborative stage [CS] schema). Cases were excluded if the primary reporting source was autopsy, death certificate, or nursing home or hospice; preferred primary reporting source was hospital inpatient data. Patients were also excluded if they were diagnosed before age 18. Cases had to have been diagnosed with microscopic confirmation, by histology or cytology. Finally, inclusion required thymoma diagnosis as the first and only malignancy, to use cancer specific survival as CSS.

Masaoka–Koga staging was approximated using an approach modeled after that used by Fernandes et al.[8] in their study of the role of radiation therapy in thymoma using SEER data. Cases were categorized into four stage groupings (Table 1): I to IIA ("invasive tumor confined to gland of origin" or "localized, not otherwise specified"), IIB ("adjacent connective tissue"), III to IV ("adjacent organs/structures" or "further contiguous extension" or any positive lymph nodes), and unknown (unknown extent of disease). These four stage groupings may be loosely referred to as "localized," "regional," "distant," and "unknown" for the remainder of this discussion. If no positive lymph nodes were indicated, then they were assumed to be negative and did not automatically result in an Unknown stage assignment.

SAS v9.3 (SAS Institute Inc., Cary, NC) was used to extract data, select cases, define variables, and for Kaplan–Meier survival analysis with log-rank tests for significance. Significance was set at a probability value less than 0.05. SAS was also used for multivariable regression using the Cox proportional hazards model. R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for creating the table of baseline demographic and thymoma characteristics, which compared continuous variables across stages by the analysis of variance test and categorical variables across stages by the χ^2 test. Microsoft Excel 2010 was used to create the conditional survival tables.

OS was defined as the time from diagnosis until death. CSS was defined according to the National Cancer Institute as the time from diagnosis until death caused by thymoma (because patients with any other cancer diagnosis were excluded). Conditional survival is the probability of surviving additional time y after already surviving time x, and can be calculated from OS or CSS using the formula: $CS(y|x) = S(x + y)/S(x)$, where $S(t)$ is the OS or CSS at time t. This study calculated 5-year conditional survival for both OS and CSS. So for instance, the 5-year conditional OS at 3 years is the probability of a patient who has already survived 3 years to live for an additional 5 years, also known as to have at least 8 years of OS. The 5-year conditional OS at 0 year is the same as the OS. OS and CSS were stratified by stage and compared across stages by the log-rank test for significance; 5-year conditional OS and 5-year conditional CSS were also stratified by stage.

RESULTS

A total of 2182 patients with thymoma were identified from the SEER (1973–2011) data set as meeting inclusion criteria. Masaoka stage group was I and IIA in 520 (24%), IIB in 350 (16%), III and IV in 1096 (50%), and unknown in 216 (10%). Patients in these stage groups were significantly different in multiple demographic (geographic region in the United States) and thymoma (grade, World Health Organization type, maximum tumor diameter, year and method of diagnosis, type of treatment) characteristics, as shown in Table 2. Unknown stage was diagnosed earlier ($p < 0.0001$), with median year of diagnosis of 1990, compared with the other stages' 2005, 2004, and 2002, and had 49% cancer death, compared with other

TABLE 1. Masaoka–Koga Stage Definitions, Compared with the Stage Groupings Assigned Using Tumor Information from SEER Data

Masaoka–Koga Staging System[5]	Stage Groupings from SEER Data (Adapted from Fernandes et al.[8])
I: Grossly and microscopically completely encapsulated tumor	"Localized": "invasive carcinoma confined to gland of origin" or "localized, not otherwise specified"
IIA: Microscopic transcapsular invasion	
IIB: Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium	"Regional": "adjacent connective tissue"
III: Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)	"Distant": "adjacent organs/structures" or "further contiguous extension" or any positive lymph nodes
IVA: Pleural or pericardial metastases	
IVB: Lymphogenous or hematogenous metastasis	

TABLE 2. Baseline Characteristics of Stage Groups and of the Whole Cohort

	Stages I and IIA		Stage IIB		Stages III and IV		Unknown			Total	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**	***P* value**	**Median**	**Range**
Age at diagnosis	57	18–89	57	21–91	56	18–90	55	19–89	0.8101	56	18–91
Year of diagnosis	2005	1973–2011	2004	1973–2011	2002	1973–2011	1990	1973–2011	*≤0.0001*	2003	1973–2011
Size in mm (imputed)	60	0–900	70	3–240	72	0–989	70	3–170	*≤0.0001*	70	0–989
	Count	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	***P* value**	**Count**	**%**
Gender											
Female	269	52	150	43	510	47	97	45	0.0561	1026	47
Male	251	48	200	57	586	53	119	55		1156	53
Race											
White	353	68	232	66	711	65	155	72	0.2359	1451	67
Black	66	13	48	14	190	17	31	14		335	15
Asian/Pac Islander	92	18	65	19	183	17	28	13		368	17
Other	9	2	5	1	12	1	2	1		28	1
Relationship status											
Single	83	16	62	18	200	18	36	17	0.2456	381	17
Married	308	59	227	65	646	59	126	58		1307	60
Separated/divorced	55	11	28	8	99	9	18	8		200	9
Widowed	47	9	23	7	114	10	24	11		208	10
Unknown	27	5	10	3	37	3	12	6		86	4
Region											
West	254	49	177	51	602	55	96	44	*0.0002*	1129	52
Central	57	11	40	11	125	11	47	22		269	12
Northeast	117	23	77	22	186	17	44	20		424	19
South	92	18	56	16	183	17	29	13		360	17
Hist confirm											
Cytology/not otherwise specified	3	1	3	1	30	3	12	6	*0.0001*	48	2
Histology	517	99	347	99	1066	97	204	94		2134	98
Grade											
Grades I and II	48	9	18	5	60	5	3	1	*≤0.0001*	129	6
Grades III and IV	17	3	9	3	80	7	9	4		115	5
Unknown	455	88	323	92	956	87	204	94		1938	89
WHO type											
Not otherwise specified	244	47	163	47	643	59	180	83	*≤0.0001*	1230	56
A	39	8	30	9	38	3	6	3		113	5
AB	72	14	47	13	80	7	6	3		205	9
B1	52	10	34	10	97	9	9	3		192	9
B2	52	10	33	9	88	8	5	2		178	8
B3	61	12	43	12	150	14	10	5		264	12
Radbeam											
Other/not otherwise specified	298	57	129	37	447	41	113	52	*≤0.0001*	987	45
Beam RT	222	43	221	63	649	59	103	48		1195	55
Treatment											
No treatment	29	6	11	3	163	15	58	27	*≤0.0001*	261	12
RT	23	4	18	5	158	14	41	19		240	11
Surgery	258	50	114	33	240	22	47	22		659	30
Surgery + RT	199	38	202	58	486	44	56	26		943	43
Unknown	11	2	5	1	49	4	14	6		79	4
Order											
Not both Surgery + RT	320	62	147	42	605	55	159	74	*≤0.0001*	1231	56
Surgery then RT	193	37	195	56	440	40	53	25		881	40
Unknown	7	1	8	2	51	5	4	2		70	3

(*Continued*)

TABLE 2. (*Continued*)

	Count	%	Count	%	Count	%	Count	%	*P* value	Count	%
Cause of death											
Alive	381	73	238	68	519	47	52	24	*≤0.0001*	1190	55
Cancer death	63	12	43	12	358	33	106	49		570	26
Noncancer death	76	15	69	20	219	20	58	27		422	19

Categorical variables were compared across stage groups using the χ^2 test. Continuous variables were compared across stage groups using the analysis of variance. Italics indicate statistically significant *P* values (<0.05).
RT, radiation therapy, WHO, World Health Organization.

groups' 12%, 12%, and 33%. Lower stages tended to have lower grades and more favorable World Health Organization types.

Fifteen years of OS data (Fig. 1) were used to calculate 5-year conditional OS (Fig. 2). Fifteen years of CSS data (Fig. 3) were used to calculate 5-year conditional CSS (Fig. 4). Localized and regional stages had significantly better OS than distant or unknown stages ($p < 0.0001$). The same pattern was true for CSS ($p < 0.0001$). Five-year conditional OS and 5-year conditional CSS were relatively stable over time across all stages. Conditional survivals were more similar between localized and regional stages and between distant and unknown stages. Five-year conditional OS ranged in 80% for localized stage, compared with 70% for regional, 60% for distant, and 50% for unknown stages. There was a slight rise and fall of 5-year conditional OS, peaking at 90% at 6 years. Five-year conditional CSS ranged in 90% for localized and regional stages, high 70% for distant, and 70% for unknown stages. There was no significant increase in conditional survivals over time, even at 10 years after diagnosis.

DISCUSSION

To our knowledge, this is the first published article to address conditional survival and the largest study of patients with malignant thymoma, including 2182 patients from the SEER registry (1973–2011). Patients can live for decades after thymoma diagnosis. Because of the indolent nature of this disease, conditional survival can be particularly valuable for patients, family, and caregivers. When the patient survives for more than 1 year, conditional survival quantifies the patient's expected survival over time, which changes every year. After every additional year the patient survives, conditional survival provides more relevant prognostic information than the more often reported survival estimates. Conditional survival estimates are also higher than static survival probabilities. For instance, CSS at 15 years for a patient with stages III and IV thymoma is 46%, but 5-year conditional CSS for the patient who has already survived to the ten year is 81%. These more accurate prognoses can help patients and their families emotionally and psychologically. Anyone can easily understand 5-year conditional survivals.

Conditional survival analysis can also help provide evidence for determining optimal follow-up testing, frequency, and duration. Duration of patient surveillance is not only important for survivorship, treatment decisions, and ensuring adequate surveillance times in retrospective data, but also for planning potential prospective studies because clinical trial duration is

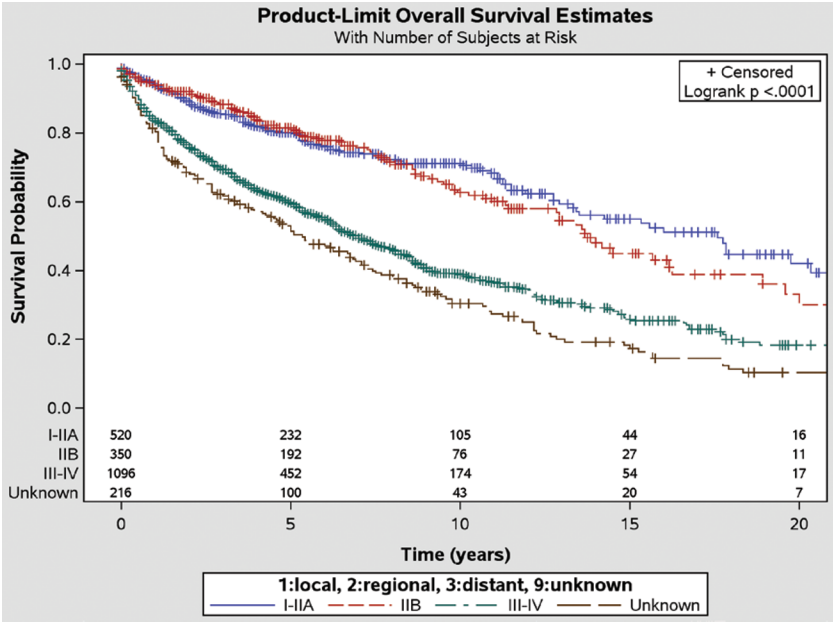
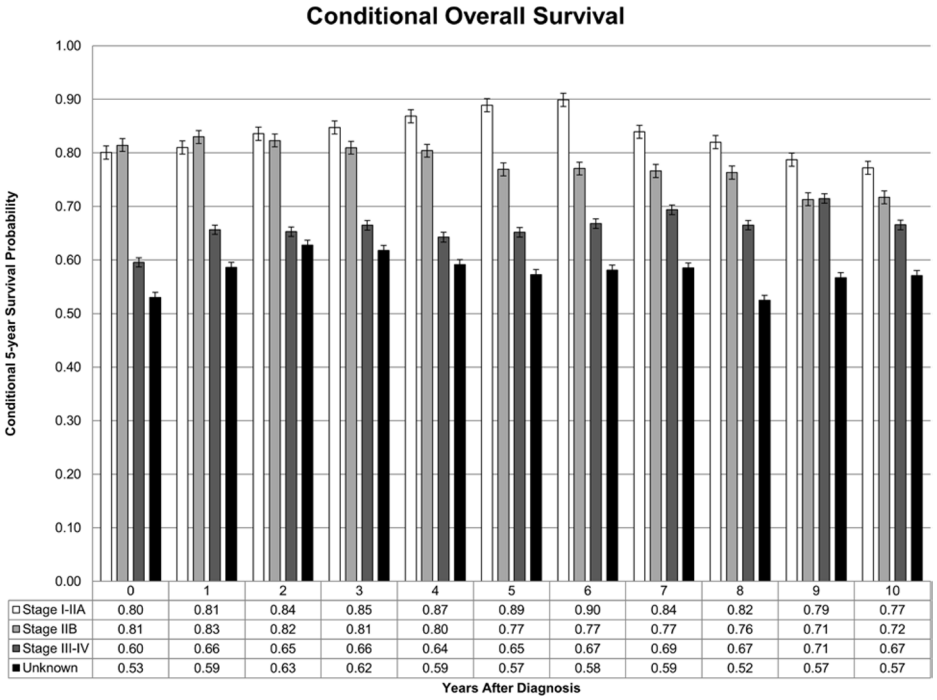


FIGURE 1. Kaplan–Meier curve of overall survival of thymoma patients by Masaoka–Koga stage group during twenty years of follow-up. These data were used to calculate the 5-year conditional OS probabilities.



	0	1	2	3	4	5	6	7	8	9	10
Stage I-IIA	0.80	0.81	0.84	0.85	0.87	0.89	0.90	0.84	0.82	0.79	0.77
Stage IIB	0.81	0.83	0.82	0.81	0.80	0.77	0.77	0.77	0.76	0.71	0.72
Stage III-IV	0.60	0.66	0.65	0.66	0.64	0.65	0.67	0.69	0.67	0.71	0.67
Unknown	0.53	0.59	0.63	0.62	0.59	0.57	0.58	0.59	0.52	0.57	0.57

FIGURE 2. Five-year conditional overall survival of thymoma patients by Masaoka–Koga stage group. Each cluster of graphs represents the probability of surviving an additional 5 years, after having already survived for 0 to 10 years after diagnosis.

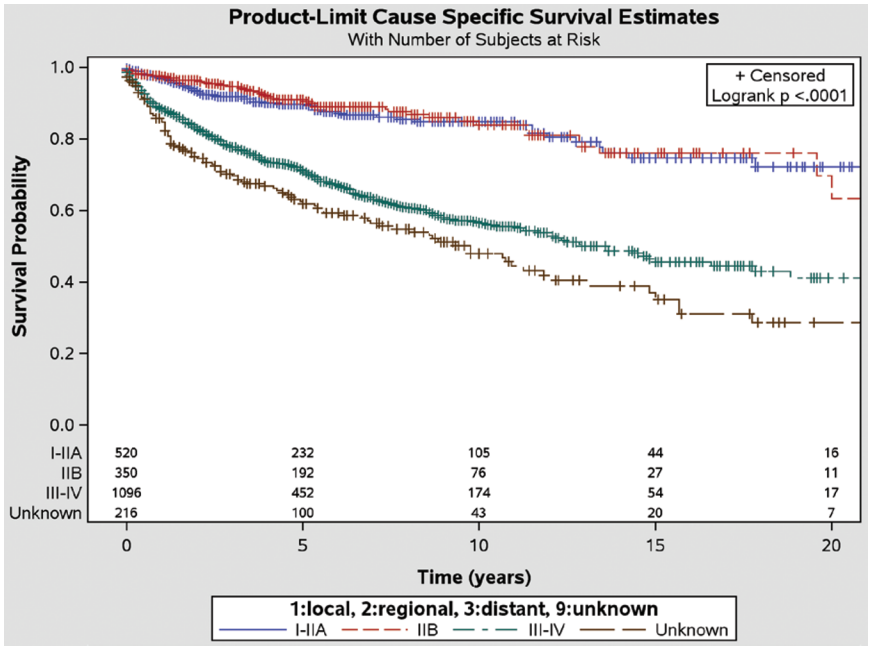
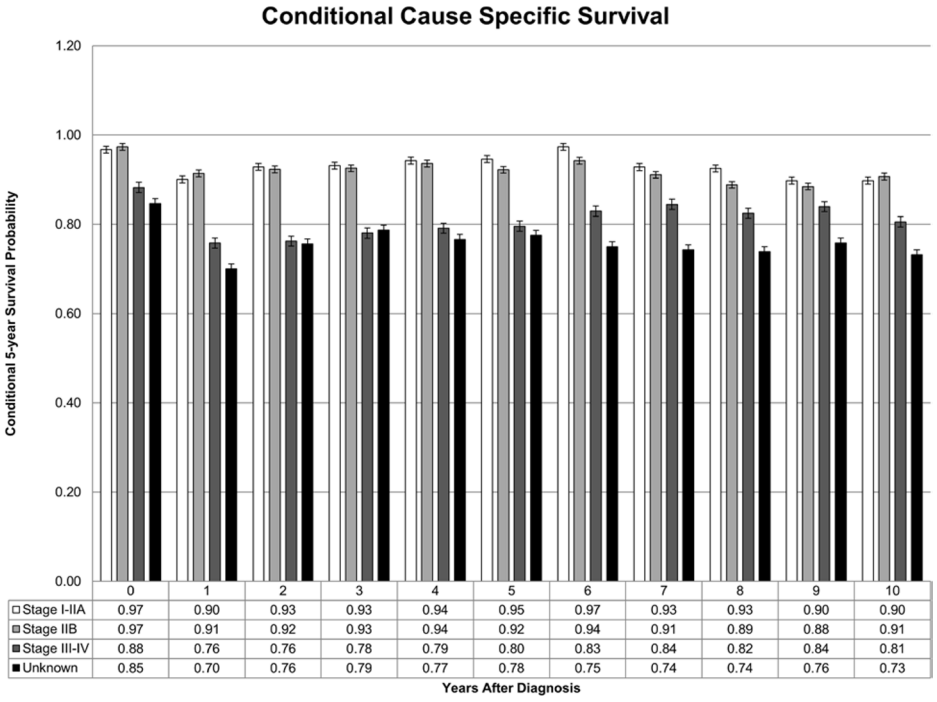


FIGURE 3. Kaplan–Meier curve of cause specific survival of thymoma patients by Masaoka–Koga stage group during 20 years of follow-up. These data were used to calculate the 5-year conditional cause specific survival probabilities.

significant in estimating economic costs and planning timelines. As part of the patient-centered care approach, the ability to reference conditional survival helps quantify the remaining risk to patients and families after a specific survival period. In addition, examining changes in this risk over time could aid in the design of prospective clinical trials for thymoma.

The original staging system published by Masaoka et al.[4] in 1981 had 65% stage I, 25% stage II, 5% stage III, and 5% stage IV. This does not resemble the distribution of Masaoka–Koga stage distributions in our study. However, our distribution is very similar to that by Fernandes et al.,[8] which is expected because we used the same method of stage grouping with updated data (1973–2003 vs. 1973–2011). About half of our cases were in stage groups III and IV, whereas Masaoka's original cohort was 65% stage I. It is possible that SEER coders preferentially included higher stage cases because SEER only includes malignant thymoma and the general confusion over what constitutes malignant thymoma.

Although the overall quality of the SEER registry is impressive, sometimes more rare tumors can have missing or



	0	1	2	3	4	5	6	7	8	9	10
Stage I-IIA	0.97	0.90	0.93	0.93	0.94	0.95	0.97	0.93	0.93	0.90	0.90
Stage IIB	0.97	0.91	0.92	0.93	0.94	0.92	0.94	0.91	0.89	0.88	0.91
Stage III-IV	0.88	0.76	0.76	0.78	0.79	0.80	0.83	0.84	0.82	0.84	0.81
Unknown	0.85	0.70	0.76	0.79	0.77	0.78	0.75	0.74	0.74	0.76	0.73

FIGURE 4. Five-year conditional cause specific survival of thymoma patients by Masaoka–Koga stage group. Each cluster of graphs represents the probability of surviving an additional 5 years, after having already survived for 0 to 10 years after diagnosis.

less reliable coding because they are encountered so rarely.[7] One example of this is an absence of comment about lymph node status. Any positive lymph nodes were categorized as distant stage; but both no indication and negative lymph nodes were treated equivalently (as negative). A nonspecific limitation of SEER data is patient migration out of SEER regions (although more than 25% of the US population is included in SEER, almost 75% is not). Finally, there is also the unavoidable selection bias of all retrospective studies. Though these limitations may have played a role in the selection of patients available for this analysis, we remain confident in the method of Masaoka–Koga stage groupings based on details available in the SEER data (Table 1).

We chose to include patients with unknown stage group because this comprised 10% of our limited cohort. It is interesting that they ended up having the poorest survivals, with a higher rate of death from thymoma. It could be related to improvement in treatments and increased availability of diagnostic imaging techniques, such as computed tomography (CT) or 18-fluoro-deoxyglucose positron emission tomography over time because the unknown group was diagnosed at a median 12–15 years earlier than the other stages. Historical data may not reflect current practices in oncology. A study of thymoma patients identified from the Swedish Cancer Registry found significant ($p < 0.01$) improvement in OS comparing cases of thymoma diagnosed in Swedish Cancer Registry in three time periods: 1958–1972, 1973–1987, and 1988–2004.[9]

Masaoka staging has been shown to be a significant prognostic factor of OS and CSS, which was also reflected in our results. Although OS is the most often reported measure of survival probability, CSS can be more meaningful for treatment planning because it excludes nonthymoma causes of death and provides more disease-specific prognosis. Localized and regional stage groups had better OS ($p < 0.0001$) and CSS ($p < 0.0001$).

Conditional survival has already been used to study several other types of cancer. Conditional relative survival of ovarian cancer improved steadily over the first 5 years of diagnosis across all stages.[10] Stage IV ovarian cancer, with the poorest 5-year conditional OS, improved from 17% at diagnosis to 56% at 5 years, and even stage I steadily improved from 90% to 95% over the first 5 years.[10] Rectal cancer showed an identical pattern of steadily increasing conditional OS over the first 5 years, where stage I improved from 73% to 74% and stage IV improved from 6% to 48%.[11] The same pattern of trends, with steady improvement over 5 years and greatest improvement from higher stages, has been seen in colon cancer,[12] gastric cancer,[13] head and neck squamous cancer,[14] and non–small-cell lung cancer.[15] Patients are often told that they are "cured" of their cancer if they survive for a certain number of years. This is supported by conditional survival analysis in many types of cancer, as mentioned above. Even distantly metastatic gastric cancer, for instance, with 2% conditional relative survival at diagnosis, has after 5 years of survival a conditional relative survival of 64% (which is better than the 61% relative survival of localized gastric cancer at diagnosis).[13]

Note that the conditional survival analyses of these other cancer sites stop after 5 years of conditional survival calculations. Five-year conditional survival at 5 years actually requires sufficient numbers of patients to survive at least 10 years, which can be difficult for most cancers, especially at later stages. This is a marked difference for thymoma, which has a long natural history. Survival after thymoma diagnosis can regularly be measured in decades, unlike most other cancers. We were able to display conditional survival even at 10 years.

Over 10 years, unlike the other cancer sites, conditional OS and conditional CSS did not change significantly in any of the stage groups. However, despite the lack of improvement over time, the 5-year conditional survival rates were still relatively high compared with other tumors especially in advanced stages, ranging from approximately 60% to 90% and 70% to 95% for conditional OS and conditional CSS, respectively. These results indicate that the risk of death, whether from thymoma or any cause, does not change significantly over time in patients diagnosed with thymoma (or at least, not in the first decade after diagnosis). As prognosis does not improve over time, it suggests that even after 10 years, patients are not truly "cured." This observation could be interpreted to suggest that patients should continue to follow-up annually with their oncologist for more than 10 years, because their risk is equivalent at diagnosis and at 10 years after diagnosis. The National Comprehensive Cancer Network guidelines recommend at least 10 years of surveillance because thymoma can have late recurrence. However, by their own acknowledgment, this recommended surveillance duration has not been established by published studies.[16] Perhaps, malignant thymoma should be considered as more of a chronic disease than as a curable cancer. Or, even longer follow-up is needed before the improvement in conditional survival is evident. Future studies should try to continue to focus on large groups of thymoma patients with even longer follow-up times.

Someone could argue that as conditional survival is relatively high, with survival rates close to "cured" conditional survival of other cancers, perhaps thymoma patients do not require annual chest CT (after chest CT every 6 months for the first 2 years). However, the results of this study do not support this argument because of the high risk of thymoma recurrence. Survival is likely high in part because of early detection of recurrences in close surveillance. Unfortunately, disease recurrence is not recorded in SEER data.

In summary, conditional survival can be particularly useful for thymoma patients. Earlier Masaoka–Koga stage groups had significantly better OS and CSS. Five-year conditional OS and CSS did not improve over the first 10 years after diagnosis, suggesting thymoma may be more of a chronic disease than a curable cancer. Additional study is needed with follow-up times longer than 20 years.

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